TABLE OF CONTENTS

I. REAL PARTY IN INTEREST

The Real Party in Interest in the instant application is Watson Pharmaceuticals, Inc., the assignee of record. Pfizer, Inc. is also a Real Party in Interest as the sole licensee of the instant application.

II. RELATED APPEALS AND INTERFERENCES

There are no prior or pending Appeals, Judicial Proceedings or Interferences known to the Appellant which may be related to, directly affect or be directly affected by or have bearing on the Board's decision in the instant appeal.

III. STATUS OF CLAIMS

Claims 1, 2, 6-13, 15-16, 20-21 have been canceled.

Claims 3-5, 14, 17-19, and 22-39 stand rejected.

Claim 40 has not been canceled, withdrawn, rejected, objected to, or indicated as allowable.

IV. STATUS OF AMENDMENTS

There have been no amendments filed subsequent to the December 7, 2006 final rejection. In the rejection, the Examiner did not address claim 40, which was newly added in the Applicant's Reply dated September 6, 2006. The Examiner also failed to acknowledge the cancellation of claims 20-21. Instead, in the Final Action, the Examiner rejected the claims which had been canceled in the September 6, 2006 Reply along with the pending claims. The Examiner's failure to address these claims is evidenced in the Office Action Summary (PTOL-326) and the Detailed Action, both of which were dated December 7, 2006.

V. SUMMARY OF THE CLAIMED SUBJECT MATTER

Independent claim 3 pertains to a transdermal formulation comprising an adhesive drug matrix reservoir and an effective amount of lasofoxifene or a pharmaceutically acceptable salt thereof (*See* application page 3, lines 18-28).

Independent claim 14 pertains to a device for administering an active agent to the skin or mucosa of an individual comprising a laminated composite of:

- a backing layer defining an upper portion of a reservoir and extending to the periphery of a peel seal disk (*See* application page 10, lines 26-28);
- an active agent-permeable membrane extending to the periphery of the peel seal disk and the backing layer, and underlying the backing layer, the backing layer and membrane defining (*See* application page 10, lines 28-30);
- the reservoir therebetween that contains a transdermal formulation comprising an effective amount of lasofoxifene or a pharmaceutically acceptable salt thereof (*See* application page 10, lines 30-31);
- the peel seal disc underlying an active agent-permeable membrane (*See* application page 10, line 31);
- a heat seal about the periphery of the peel seal disc, the active agent-permeable membrane and the backing layer (*See* application page 10, lines 31-33);
- an adhesive overlay having a central portion overlying the backing layer and a peripheral portion that extends beyond the periphery of the peel seal disc (*See* application page 10, line 35); and
- a removable release liner underlying the peripheral portion of the adhesive overlay and the peel seal disc (*See* application page 11, lines 2-3).

Independent claim 32 pertains to a method for treating or preventing a disorder associated with estrogen deficiency or disregulation in a subject comprising contacting an application situs of the subject with a transdermal formulation comprising a free form hydroalcoholic gel and an effective amount of lasofoxifene or a pharmaceutically acceptable salt thereof (*See* application page 11, lines 4-7 and page 12, lines 3-8).

Independent claim 36 pertains to a method for treating or preventing a disorder associated with estrogen deficiency or disregulation in a subject comprising contacting an application situs of the subject with a transdermal formulation comprising a liquid reservoir drug formulation comprising an effective amount of lasofoxifene or a pharmaceutically acceptable salt thereof (*See* application page 11, lines 4-7; page 15, lines 9-15; page 16, lines 10-16; page 17, lines 8-17; and page 19, lines 8-13).

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Whether claims 3-5, 14, 17-19 and 22-39 are unpatentable under 35 U.S.C. § 103 over Cormier *et al.* (U.S. Patent No. 6,203,817) in view of Ke *et al.* (U.S. Patent No. 6,323,232).

VII. ARGUMENT

A. The Legal Standard

To establish *a prima facie* case of obviousness under 35 U.S.C. § 103(a), three basic criteria must be met: (1) there must be some suggestion or motivation to modify the reference or to combine reference teachings, (2) there must be a reasonable expectation of success, and (3) the prior art reference(s) must teach or suggest all of the claim limitations. *In re Vaeck,* 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

When applying Section 103(a), four tenets of patent law must be adhered to: (1) the claimed invention must be considered as a whole; (2) the references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination; (3) the references must be viewed without the benefit of impermissible hindsight; and (4) a reasonable expectation of success is the standard with which obviousness is determined. *Hodosh v. Block Drug Co., Inc.,* 786 F.2d 1136, 1143 (Fed. Cir. 1986).

Moreover, mere identification of each claimed element in the prior art is insufficient to negate patentability. *In Re Rouffet,* 149 F.3d 1350, 1357 (Fed. Cir. 1998). Instead, there "must be a teaching or suggestion within the prior art, or within the general knowledge of a person of ordinary skill in the filed of the invention, to look to particular sources of information, to select particular elements, and to combine them in the way they were combined by the inventor." *ATD Corp. v. Lydall, Inc.,* 159 F.3d 534, 536 (Fed. Cir. 1998). Otherwise, sophisticated scientific fields would rarely, if ever, experience a patentable technical advance. *Rouffet,* 149 F.3d at 1357.

B. Rejection of Claims 3-5 and 28-29 under 35 U.S.C. § 103 (a) over Cormier *et al.* in view of Ke *et al.*

Claims 3-5 and 28-29 stand rejected under 35 U.S.C. § 103(a) as purportedly obvious over Cormier *et al.* (US 6,203,817) in view of Ke *et al.* (US 6,323,232).

The Examiner has stated that the basis for the rejection is as follows:

> The '817 patent discloses a transdermal formulation comprising an adhesive drug matrix reservoir (abstract). The transdermal [formulation] is attached to the skin and comprises a backing layer, adhesive overlay, and a release liner all sealed together to prevent leakage (col. 9, lin. 38-58). The formulation further comprises penetration enhancers (col. 10, lin. 5-56, examples). The transdermal formulation delivers various active agents including antiestrogen and antiosteoporotic agents such as tamoxifen and raloxifene (col. 7, lin. 66-68). The reference however lacks a disclosure of lasofoxifene a similar antiestrogen agent.

See Final Action paragraph 4. The Examiner has further stated that:

> The '232 patent discloses a combination transdermal therapy including lasofoxifene and other estrogen agonists/antagonists (claim 1). Among other agents used in combination therapy are droloxifene, raloxifene and tamoxifen (col. 6, lin. 35-40). A skilled artisan would have been motivated to include the lasofoxifene of '232 into the transdermal formulation of '817 in order to impart antiosteoporotic properties onto the formulation.

See Final Action paragraph 5. Finally, the Examiner states that:

> [O]ne of ordinary skill in the art would have been motivated to combine the teachings of '232 and '217 since both teach transdermal delivery of antiestrogen agents, in order to impart the antiosteoporotic properties of lasofoxifene onto the formulation. *See* Final Action paragraph 6

Within the final rejection, the Examiner asserts that Cormier et al. discloses a reservoir, backing layer, an adhesive overlay, a release liner and permeation enhancers for the delivery of raloxifene and tamoxifen. *See* Final Action paragraph 4. The Examiner then draws the conclusion that since Cormier *et al.* discuss tamoxifen and raloxifene in a list of pharmaceuticals that encompasses a multitude of unrelated drug classes, it would have been obvious to one of ordinary skill in the art to combine any pharmaceutical having

antiestrogenic properties with the transdermal delivery formulation claimed without regard to the pharmaceutical's chemical properties. *See* Final Action paragraph 4.

Next, by performing a "Google-like" search, the Examiner apparently located Ke *et al.*, which discusses combination therapy for the treatment of osteoporosis. Ke *et al.* mentions several antiestrogenic drugs such as droloxifene, raloxifene, and tamoxifen and also separately mentions lasofoxifene in claims 1 and 2. From this disclosure, the Examiner summarily and without regard to a reasonable expectation of success asserted that it would have been obvious to combine Cormier *et al.* and Ke *et al.* to arrive at the formulations and devices of the rejected claims. *See* Final Action paragraph 5.

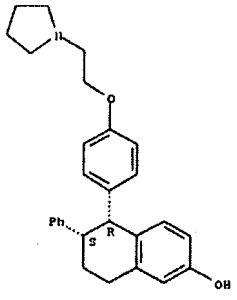
This conclusion, however, fails to note that transdermal drug delivery formulations similar to those claimed are not mentioned in either publication. The Examiner also fails to take into account the chemical properties of the pharmaceuticals and how these properties dictate their formulation. As a result, the Examiner's conclusion is based on the false presumption that drugs of the same pharmacologic class possess similar chemical properties and characteristics.

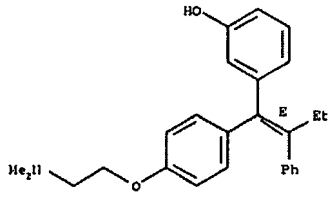
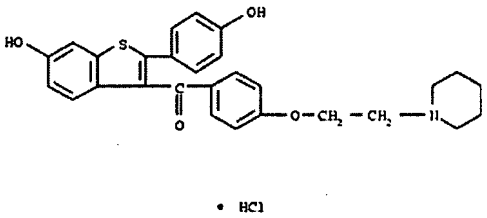
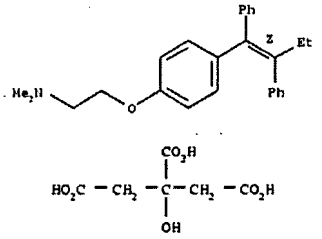
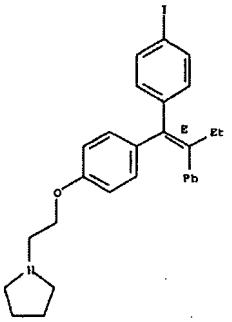
It is a well-established principle of patent law that compounds of similar *structure* are presumed to have similar properties. *See, In re Dillon*, 919 F.2d 688, 692-693; 16 U.S.P.Q. 2d 1897, 1901 (Fed. Cir. 1990). However, there is *no* legal basis for presuming the converse, *i.e.*, that compounds with similar pharmacological activities necessarily have similar chemical structures or characteristics; indeed, the opposite is true. *See, e.g., In re Jezl*, 396 F.2d 1009, 1012; 158 U.S.P.Q. 98, 99-100 (CCPA 1968) ("the mere inclusion of several compounds in a list of compounds...does not necessarily establish that each of those compounds is equivalent to the others for all purposes."). It is well known in the art that a pharmacological classification is only based the behavior a compound exhibits in the human

body and not their chemical make-up. For example, antiestrogenic compounds have a single characteristic in common: the fact that they work against the effect of estrogen *in vivo*. As a result of this activity, they are listed together under the pharmacologic class of antiestrogenic compounds. The Examiner's rejection, however, assumes that all of the antiestrogenic compounds listed are equivalent for purposes of formulating a transdermal drug delivery device. This assumption is in direct contradiction well-settled principles of pharmacology and case law.

Contrary to the statements within the December 9, 2006 Office Action, the pharmaceuticals considered by the Examiner are, in fact, quite different. The varying chemical structures and functional groups (as shown below) present within these pharmaceuticals affect such properties as the stability of the active ingredient, stability of the adjuvant in combination with the active ingredient, phase distribution within the matrix, pH, and release from the matrix and bioavailability. These properties, in turn, complicate the formulation of a transdermal drug delivery device.

To better demonstrate the structural differences between the compounds cited by the Examiner and how their behavior in matrix systems cannot be equated with the claimed compound, the following table shows the chemical structure of the cited compounds.

Pharmaceutical Name	Chemical Structure	Source Patent/Primary Classification
Lasofoxifene (claimed compound)		U.S. Patent No. 5,552,412 U.S. Cl. 514/317

Pharmaceutical Name	Chemical Structure	Source Patent/Primary Classification
Droloxifene		U.S. Patent No. 5,047,431 U.S. Cl. 514/648
Raloxifene HCl		U.S. Patent No. 4,418,068 U.S. Cl. 424/267
Tamoxifen citrate		U.S. Patent No. 4,536,516 U.S. Cl. 514/514
Idoxifene		U.S. Patent No. 4,839,155 U.S. Cl. 424/1.1

This diverse group of compounds naturally have differing chemical properties that affect their formulation, as each compound has differing functional groups (e.g., piperidine, pyrrolidine, thiophene, phenol, carboxylic acid and halogenated aromatic groups). These functional groups impart different chemical and physical characteristics in the transdermal system as presently claimed. This is confirmed by reviewing the primary classification

assigned to the U.S. Patents which claim these particular compounds. The fact that each of these patents has a different primary classification demonstrates that the USPTO recognizes the differences between these compounds.

In addition, Ke *et al.* neither discloses nor suggests transdermal drug delivery formulations that are at all similar to those claimed by Applicants. In fact, the disclosure in Ke *et al.* can hardly be considered to be a transdermal formulation because it is no different than an intravenous solution. For example, Ke *et al.* state that "[f]or purposes of transdermal (e.g., topical) administration, dilute sterile, aqueous or partially aqueous solutions (usually in about 0.1% to 5% concentration), otherwise similar to the above parenteral solutions, are prepared" (*see* column 37, lines 49-52). Thus, Ke *et al.* teaches that topical transdermal administration is performed using a solution. Ke *et al.* does not teach anything close to the presently claimed transdermal delivery formulation containing a matrix, a hydroalcoholic gel or a liquid reservoir from which lasofoxifene is continuously released providing systemic bioavailability. Nor does Ke *et al.* mention or consider any of the factors that must be taken into account when formulating pharmaceuticals for transdermal delivery as presently claimed.

With these considerations in mind, one of ordinary skill in the art would not be motivated to combine the publications as the Examiner has suggested because the compounds above would be expected to have dramatically different chemical properties requiring unique formulations that will necessarily affect their formulation in a drug matrix, hydroalcoholic gel or liquid reservoir. In fact, the differing chemical structures and properties of tamoxifen and raloxifene as compared to lasofoxifene actually *teach away* from combining lasofoxifene with the transdermal delivery system discussed in Cormier *et al.* because the compounds are so structurally different that one of ordinary skill would not reasonably expect them to behave

in the same manner according to their chemical characteristics when formulated into a drug matrix.

As a result, the Examiner has not set forth a *prima facie* case of obviousness because no motivation exists in the art to combine the cited publications, because there is no discussion of how one of skill would have a reasonable expectation of success, and because the Examiner's argument does not take into account the variable chemical characteristics of the compounds cited in the publications and the difficulty in formulating drug delivery devices with such compounds. For all these reasons, it is respectfully requested that this rejection be withdrawn.

C. Rejection of Claims 17 and 22-24 under 35 U.S.C. § 103 (a) over Cormier *et al.* in view of Ke *et al.*

Claims 17 and 22-24 stand rejected under 35 U.S.C. § 103(a) as purportedly obvious over the combined disclosures of Cormier *et al.* (US 6,203,817) and Ke *et al.* (US 6,323,232).

The Examiner has stated that the basis for the rejection is as follows:

> The '817 patent discloses a transdermal formulation comprising an adhesive drug matrix reservoir (abstract). The transdermal [formulation] is attached to the skin and comprises a backing layer, adhesive overlay, and a release liner all sealed together to prevent leakage (col. 9, lin. 38-58). The formulation further comprises penetration enhancers (col. 10, lin. 5-56, examples). The transdermal formulation delivers various active agents including antiestrogen and antiosteoporotic agents such as tamoxifen and raloxifene (col. 7, lin. 66-68). The reference however lacks a disclosure of lasofoxifene a similar antiestrogen agent.

See Final Action paragraph 4. The Examiner further states that:

> The '232 patent discloses a combination transdermal therapy including lasofoxifene and other estrogen agonists/antagonists (claim 1). Among other agents used in combination therapy are droloxifene, raloxifene and tamoxifen (col. 6, lin. 35-40). A skilled artisan would have been motivated to include the lasofoxifene of '232 into the transdermal formulation of '817 in order to impart antiosteoporotic properties onto the formulation.

See Final Action paragraph 5. Finally, the Examiner concludes that:

> [O]ne of ordinary skill in the art would have been motivated to combine the teachings of '232 and '217 since both teach transdermal delivery of antiestrogen agents, in order to impart the antiosteoporotic properties of lasofoxifene onto the formulation.

See Final Action paragraph 6.

The standard for establishing a *prima facie* case of obviousness is discussed in § VII. A., above.

Claims 17 and 22-24 are not *prima facie* obvious over the cited publications for the same reasons discussed above with respect to claims 3-5 and 28-29. Additionally, claims 17 and 22-24 are not *prima facie* obvious since the Examiner has failed to show how the cited publications disclose or suggest the methods of treatment and prevention of claims 17 and 22-24.

As a result, the Examiner has not met the basic requirements for establishing a *prima facie* case of obviousness. Therefore, with regard to the claimed methods of treatment or prevention of a disorder associated with estrogen deficiency or disregulation, the Examiner has not made out a *prima facie* case that Cormier *et al.*, Ke *et al.* or any other publication teaches or suggests the methods of the rejected claims. The very fact that the Examiner has only identified some of the claimed elements in the publications demonstrates that these arguments are insufficient to negate patentability. Accordingly, since the rejection has been overcome, it is respectfully requested that this rejection be withdrawn.

D. Rejection of Claims 30-31 under 35 U.S.C. § 103 (a) over Cormier *et al.* in view of Ke *et al.*

Claims 30-31 stand rejected under 35 U.S.C. § 103(a) as being obvious over the combined disclosures of Cormier *et al.* (US 6,203,817) and Ke *et al.* (US 6,323,232).

The Examiner has stated that the basis for the rejection is as follows:

> The '817 patent discloses a transdermal formulation comprising an adhesive drug matrix reservoir (abstract). The transdermal [formulation] is attached to the skin and comprises a backing layer, adhesive overlay, and a release liner all sealed together to prevent leakage (col. 9, lin. 38-58). The formulation further comprises penetration enhancers (col. 10, lin. 5-56, examples). The transdermal formulation delivers various active agents including antiestrogen and antiosteoporotic agents such as tamoxifen and raloxifene (col. 7, lin. 66-68). The reference however lacks a disclosure of lasofoxifene a similar antiestrogen agent.

See Final Action paragraph 4. The Examiner further states that:

> The '232 patent discloses a combination transdermal therapy including lasofoxifene and other estrogen agonists/antagonists (claim 1). Among other agents used in combination therapy are droloxifene, raloxifene and tamoxifen (col. 6, lin. 35-40). A skilled artisan would have been motivated to include the lasofoxifene of '232 into the transdermal formulation of '817 in order to impart antiosteoporotic properties onto the formulation.

See Final Action paragraph 5. Finally, the Examiner asserts that:

> [O]ne of ordinary skill in the art would have been motivated to combine the teachings of '232 and '217 since both teach transdermal delivery of antiestrogen agents, in order to impart the antiosteoporotic properties of lasofoxifene onto the formulation.

See Final Action paragraph 6.

The standard for establishing a *prima facie* case of obviousness is set forth in § VII.A., above.

Claims 30 and 31 are not *prima facie* obvious over the cited publications for the same reasons discussed above with respect to claims 3-5, 17, 22-24, and 28-29. Additionally,

claims 30 and 31 are not *prima facie* obvious since the Examiner has failed to show how the cited publications disclose or suggest each of the limitations of claims 30 and 31.

With regard to the independent claims from which these claims depend, the Examiner asserts that Cormier *et al.* disclose a reservoir, backing layer, an adhesive overlay, a release liner and permeation enhancers for the delivery of raloxifene and tamoxifen. *See* Final Action paragraph 4. However, the Examiner's recitation of claim limitations fails to address all of the elements of claims 30 and 31 with either of the two publications cited. In particular, with regard to the transdermal formulation in dependent claim 30, the Examiner has not cited any publication describing an effective amount of a cell-envelope disordering compound as required by Claim 30, nor how a method using such a compound would be obvious. As a result, the Examiner has not fulfilled one of the basic requirements for a *prima facie* case of obviousness since every claim element is not accounted for in any of the publications cited or in the state of the art. Therefore, in regard to the methods of treatment claimed, Cormier *et al.* does not teach or suggest all of the limitations claimed and the missing claim limitations are not supplied by a secondary publication as required by *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

As a result, the Examiner has not set forth a *prima facie* case of obviousness because the cited publications simply do not teach or suggest all of the limitations of the rejected claims. The very fact that the examiner has only identified some of the claimed elements in the publications demonstrates that these arguments are not sufficient to negate patentability. Accordingly, since the rejection has been overcome, it is respectfully requested that this rejection be withdrawn.

E. Rejection of Claims 14, 18-19, 25, and 27 under 35 U.S.C. § 103 (a) over Cormier *et al.* in view of Ke *et al.*

Claims 14, 18-19, 25, and 27 stand rejected under 35 U.S.C. § 103(a) as purportedly obvious over the combined disclosures of Cormier *et al.* (US 6,203,817) and Ke *et al.* (US 6,323,232).

The Examiner has stated that the basis for the rejection is as follows:

> The '817 patent discloses a transdermal formulation comprising an adhesive drug matrix reservoir (abstract). The transdermal [formulation] is attached to the skin and comprises a backing layer, adhesive overlay, and a release liner all sealed together to prevent leakage (col. 9, lin. 38-58). The formulation further comprises penetration enhancers (col. 10, lin. 5-56, examples). The transdermal formulation delivers various active agents including antiestrogen and antiosteoporotic agents such as tamoxifen and raloxifene (col. 7, lin. 66-68). The reference however lacks a disclosure of lasofoxifene a similar antiestrogen agent

. *See* Final Action paragraph 4. The Examiner further states that:

> The '232 patent discloses a combination transdermal therapy including lasofoxifene and other estrogen agonists/antagonists (claim 1). Among other agents used in combination therapy are droloxifene, raloxifene and tamoxifen (col. 6, lin. 35-40). A skilled artisan would have been motivated to include the lasofoxifene of '232 into the transdermal formulation of '817 in order to impart antiosteoporotic properties onto the formulation..

See Final Action paragraph 5. Finally, the Examiner concludes that:

> [O]ne of ordinary skill in the art would have been motivated to combine the teachings of '232 and '217 since both teach transdermal delivery of antiestrogen agents, in order to impart the antiosteoporotic properties of lasofoxifene onto the formulation. *See* Final Action paragraph 6.

The standard for establishing a *prima facie* case of obviousness is set forth in § VII.A. above.

Claims 14, 18-19, 25, and 27 are not *prima facie* obvious over the cited publications for all of the reasons discussed above with respect to claims 3-5, 17, 22-24, and 28-29. In addition, claims 14, 18-19, 25 and 27 are not *prima facie* obvious over the cited publications

because the rejected claims contain additional limitations not discussed by the Examiner in setting forth his rejection of the claims.

As noted above, the Examiner asserts that Cormier *et al.* disclose a reservoir, backing layer, an adhesive overlay, a release liner and permeation enhancers for the delivery of raloxifene and tamoxifen. *See* Final Action paragraph 4. However, with respect to the transdermal formulation of independent claim 14 (and of claims 18-19, 25, and 27 which depend therefrom), the Examiner has not cited any publication describing claim elements such as the peel seal disc underlying the active agent permeable membrane, the heat seal about the periphery of the peel seal disc and the removable release liner. As a result, the Examiner has not fulfilled one of the basic requirements for a *prima facie* case of obviousness since several claim elements are not accounted for in any of the publications cited. Therefore, with regard to the transdermal delivery formulation of claims 14, 18-19, 25, and 27, Cormier *et al.* does not teach or suggest all of the limitations of the rejected claims and the missing claim limitations are not supplied by a secondary publication as required by *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

As a result, the Examiner has not set forth a *prima facie* case of obviousness because a motivation to combine has not been defined in the art, there is no discussion of how one of skill would have a reasonable expectation of success, and the publications simply do not teach all of the claim limitations of the current claims. The very fact that the examiner has only identified some of the claimed elements in the publications demonstrates that these arguments are not sufficient to negate patentability. Accordingly, since the rejection has been overcome, it is respectfully requested that this rejection be withdrawn.

F. Rejection of Claims 32-35 under 35 U.S.C. § 103 (a) over Cormier *et al.* in view of Ke *et al.*

Claims 32-35 stand rejected under 35 U.S.C. § 103(a) as purportedly obvious over the combined disclosures of Cormier *et al.* (US 6,203,817) and Ke *et al.* (US 6,323,232).

The Examiner has stated that the basis for the rejection is as follows:

> The '817 patent discloses a transdermal formulation comprising an adhesive drug matrix reservoir (abstract). The transdermal [formulation] is attached to the skin and comprises a backing layer, adhesive overlay, and a release liner all sealed together to prevent leakage (col. 9, lin. 38-58). The formulation further comprises penetration enhancers (col. 10, lin. 5-56, examples). The transdermal formulation delivers various active agents including antiestrogen and antiosteoporotic agents such as tamoxifen and raloxifene (col. 7, lin. 66-68). The reference however lacks a disclosure of lasofoxifene a similar antiestrogen agent.

See Final Action paragraph 4. The Examiner further states that:

> The '232 patent discloses a combination transdermal therapy including lasofoxifene and other estrogen agonists/antagonists (claim 1). Among other agents used in combination therapy are droloxifene, raloxifene and tamoxifen (col. 6, lin. 35-40). A skilled artisan would have been motivated to include the lasofoxifene of '232 into the transdermal formulation of '817 in order to impart antiosteoporotic properties onto the formulation.

See Final Action paragraph 5. The Examiner concludes that:

> [O]ne of ordinary skill in the art would have been motivated to combine the teachings of '232 and '217 since both teach transdermal delivery of antiestrogen agents, in order to impart the antiosteoporotic properties of lasofoxifene onto the formulation.

See Final Action paragraph 5.

The standard for establishing a *prima facie* case of obviousness is set forth in § VII.A., above.

Claims 32-35 are not *prima facie* obvious over the cited publications for the same reasons discussed above with respect to with respect to claims 3-5, 17, 22-24, and 28-29.

Claims 32-35 are not *prima facie* obvious for the additional reason that the Examiner has not

pointed to any disclosure of particular limitations of the rejected claims in the cited publications.

Specifically, the Examiner asserts that Cormier *et al.* disclose a reservoir, backing layer, an adhesive overlay, a release liner and permeation enhancers for the delivery of raloxifene and tamoxifen. *See* Final Action paragraph 4. The Examiner's assertion, however, fails to address all of the claim elements. In regard to the transdermal formulation in independent claim 32 (and claims 33-35 which depend therefrom), the Examiner has not cited any publication describing a transdermal formulation comprising a free form hydroalcoholic gel. As a result, the Examiner has not set forth a *prima facie* case of obviousness because a motivation has not been defined in the art, there is no discussion of how one of skill would have a reasonable expectation of success, and the cited publications simply do not teach all of the claim limitations of the current claims. The very fact that the Examiner has only identified some of the claimed elements in the publications demonstrates that these arguments are not sufficient to negate patentability. Accordingly, since the rejection has been overcome, it is respectfully requested that this rejection be withdrawn.

G. Rejection of Claims 36-39 under 35 U.S.C. § 103 (a) over Cormier *et al.* in view of Ke *et al.*

Claims 36-39 stand rejected under 35 U.S.C. § 103(a) as being obvious over the combined disclosures of Cormier *et al.* (US 6,203,817) and Ke *et al.* (US 6,323,232).

The Examiner has stated that the basis for the rejection is as follows:

> The '817 patent discloses a transdermal formulation comprising an adhesive drug matrix reservoir (abstract). The transdermal [formulation] is attached to the skin and comprises a backing layer, adhesive overlay, and a release liner all sealed together to prevent leakage (col. 9, lin. 38-58). The formulation further comprises penetration enhancers (col. 10, lin. 5-56, examples). The transdermal formulation delivers various active agents including antiestrogen

> and antiosteoporotic agents such as tamoxifen and raloxifene (col. 7, lin. 66-68). The reference however lacks a disclosure of lasofoxifene a similar antiestrogen agent.

See Final Action paragraph 4. The Examiner further states that:

> The '232 patent discloses a combination transdermal therapy including lasofoxifene and other estrogen agonists/antagonists (claim 1). Among other agents used in combination therapy are droloxifene, raloxifene and tamoxifen (col. 6, lin. 35-40). A skilled artisan would have been motivated to include the lasofoxifene of '232 into the transdermal formulation of '817 in order to impart antiosteoporotic properties onto the formulation.

See Final Action paragraph 5. Finally, the Examiner concludes that:

> [O]ne of ordinary skill in the art would have been motivated to combine the teachings of '232 and '217 since both teach transdermal delivery of antiestrogen agents, in order to impart the antiosteoporotic properties of lasofoxifene onto the formulation.

See Final Action paragraph 5.

The standard for establishing a prima facie case of obviousness is set forth in § VII.A., above.

Claims 36-39 are not *prima facie* obvious over the cited publications for all of the reasons discussed above with respect to claims 3-5, 17, 22-24, and 28-29. In addition, claims 14, 18-19, 25 and 27 are not *prima facie* obvious over the cited publications because the rejected claims contain additional limitations not discussed by the Examiner in setting forth his rejection of the claims.

Specifically, the Examiner asserts that Cormier *et al.* disclose a reservoir, backing layer, an adhesive overlay, a release liner and permeation enhancers for the delivery of raloxifene and tamoxifen. *See* Final Action paragraph 4. The Examiner's assertion, however, fails to address all of the claim elements. In regard to the transdermal formulation in independent claim 36 (and of claims 37-39 which depend therefrom), the Examiner has not cited any publication describing a transdermal delivery device comprising liquid reservoir

drug formulation. The Examiner also does not cite any reference discussing a method of treating or preventing a disorder associated with estrogen deficiency or disregulation which meets the limitations of the instant claims. As a result, the Examiner has not fulfilled one of the basic requirements for a *prima facie* case of obviousness since several claim elements are not found within the cited publications. Therefore, in regard to the transdermal delivery formulation, Cormier *et al.* does not teach or suggest all of the limitations of the rejected claims and the missing claim limitations are not supplied by a secondary publication as required by *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

As a result, the Examiner has not set forth a *prima facie* case of obviousness because a motivation to combine the cited publications has not been defined in the art, there is no discussion of how one of skill would have a reasonable expectation of success, and the cited publications simply do not teach all of the claim limitations of the current claims. The very fact that the examiner has only identified some of the claimed elements in the publications demonstrates that these arguments are not sufficient to negate patentability. Accordingly, since the rejection has been overcome, it is respectfully requested that this rejection be withdrawn.

CONCLUSION

In view of the foregoing arguments, Applicant respectfully requests reconsideration and withdrawal of the claim rejections, and that the application be passed to issuance. Failing that, the Applicant respectfully requests the Board to overrule the Examiner's rejections, based on the explanations presented above, and to pass this application to issuance.

No fees are believed to be due at this time. Should any fee be required, however, please charge such fee to Bingham McCutchen, LLP Deposit Account No. 50-4047.

Respectfully submitted,

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VIII. CLAIMS APPENDIX

1.-2. (Canceled)

3. (Previously Amended) A transdermal formulation comprising an adhesive drug matrix reservoir and an effective amount of lasofoxifene or a pharmaceutically acceptable salt thereof.

4. (Original) The transdermal formulation of claim 3, wherein the adhesive matrix is a solvent based pressure sensitive adhesive matrix.

5. (Original) The transdermal formulation of claim 3, wherein the adhesive matrix is a water based pressure sensitive adhesive matrix.

6.-13. (Canceled)

14. (Previously Amended) A device for administering an active agent to the skin or mucosa of an individual comprising a laminated composite of:

a. a backing layer defining an upper portion of a reservoir and extending to the periphery of a peel seal disk;

b. an active agent-permeable membrane extending to the periphery of the peel seal disk and the backing layer, and underlying the backing layer, the backing layer and membrane defining;

c. the reservoir therebetween that contains a transdermal formulation comprising an effective amount of lasofoxifene or a pharmaceutically acceptable salt thereof;

d. the peel seal disc underlying an active agent-permeable membrane;

e. a heat seal about the periphery of the peel seal disc, the active agent-permeable membrane and the backing layer;

f. an adhesive overlay having a central portion overlying the backing layer and a peripheral portion that extends beyond the periphery of the peel seal disc; and

g. a removable release liner underlying the peripheral portion of the adhesive overlay and the peel seal disc.

15.-16. (Canceled)

17. (Previously Amended) A method for treating or preventing a disorder associated with estrogen deficiency or disregulation in a subject comprising contacting an application situs of the subject with an effective pharmaceutical formulation of any of claims 3 to 5.

18. (Original) A method for treating or preventing a disorder associated with estrogen deficiency or disregulation in a subject comprising contacting an application situs of the subject with the device of claim 14.

19. (Original) A method for treating or preventing a disorder associated with estrogen deficiency in a subject comprising contacting a dermal situs of the subject with the device of claim 14.

20.- 21 (Canceled)

22. (Previously Presented) The method of claim 17, wherein the pharmaceutical formulation further comprises a drug permeation enhancer.

23. (Previously Presented) The method of claim 22, wherein the drug permeation enhancer is an effective amount of cell-envelope disordering compound.

24. (Previously Presented) The method of claim 23, wherein the cell-envelope disordering compound comprises an effective amount of a lower alkanol.

25. (Previously Presented) The device of 14, wherein the pharmaceutical formulation further comprises a drug permeation enhancer.

26. (Previously Presented) The device of claim 25, wherein the drug permeation enhancer is an effective amount of cell-envelope disordering compound.

27. (Previously Presented) The device of claim 26, wherein the cell-envelope disordering compound comprises an effective amount of a lower alkanol.

28. (Previously Presented) A transdermal device comprising a means for adhering a drug reservoir to the application situs and the transdermal formulation of any of claims 3 to 5.

29. (Previously Presented) The transdermal device of claim 28, wherein the transdermal formulation further comprises an effective amount of a drug permeation enhancer.

30. (Previously Presented) The device of claim 29, wherein the drug permeation enhancer is an effective amount of cell-envelope disordering compound.

31. (Previously Presented) The device of claim 30, wherein the cell-envelope disordering compound comprises an effective amount of a lower alkanol.

32. (Previously Amended) A method for treating or preventing a disorder associated with estrogen deficiency or disregulation in a subject comprising contacting an application situs of the subject with a transdermal formulation comprising a free form hydroalcoholic gel and an effective amount of lasofoxifene or a pharmaceutically acceptable salt thereof.

33. (Previously Presented) The method of claim 32, further comprising an effective amount of a drug permeation enhancer.

34. (Previously Presented) The method of claim 33, wherein the drug permeation enhancer is an effective amount of cell-envelope disordering compound.

35. (Previously Presented) The method of claim 34, wherein the cell-envelope disordering compound comprises an effective amount of a lower alkanol.

36. (Previously Presented) A method for treating or preventing a disorder associated with estrogen deficiency or disregulation in a subject comprising contacting an application situs of the subject with a transdermal formulation comprising a liquid reservoir drug

situs of the subject with a transdermal formulation comprising a liquid reservoir drug formulation comprising an effective amount of lasofoxifene or a pharmaceutically acceptable salt thereof.

37. (Previously Presented) The method of claim 36, further comprising an effective amount of a drug permeation enhancer.

38. (Previously Presented) The method of claim 37, wherein the drug permeation enhancer is an effective amount of cell-envelope disordering compound.

39. (Previously Presented) The method of claim 38, wherein the cell-envelope disordering compound comprises an effective amount of a lower alkanol.

40. (New) The transdermal formulation of claim 3, 4, or 5, wherein the cell-envelope disordering compound comprises an effective amount of a lower alkanol.

IX. EVIDENCE APPENDIX

None.

X. RELATED PROCEEDINGS APPENDIX

None.